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Clinical Laboratory Values in Human Ebola Virus Disease Support the Relevance of the Intramuscular Ebola-Kikwit Rhesus Model

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Ethics Statement: Animal research at U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) was conducted under an Institutional Animal Care and Use Committee (IACUC) approved protocol in compliance with the Animal Welfare Act, PHS Policy, and other federal statutes and regulations relating to animals and experiments involving animals. The facility where this research was conducted is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International and adheres to principles stated in the Guide for the Care and Use of Laboratory Animals, National Research Council, 2011.

To the EDITOR – We read with interest the recent article in Clinical Infectious Diseases by Lanini et al, which focused on the relationship between human Ebola Virus (EBOV) RNA and clinical chemistry values obtained during the West African outbreak in Goderich, Sierra Leone [1]. While many investigators have demonstrated that EBOV viremia is associated with survival [2-6], Lanini et al. found that multilevel mixed effect regression models demonstrated a significant correlation between EBOV viremia and aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine phosphokinase (CPK), lactate dehydrogenase (LDH), international normalized ratio (INR), and adjusted partial thromboplastin time (aPTT). This is important because these findings further support the possibility of using human clinical laboratory values as surrogate markers of EBOV viral load as Janvier et al. suggested with regard to AST [7]. Moreover, we recently published that in a linear regression model at 5 days post-infection (dpi) in rhesus macaques exposed to 1000 plaque forming units (pfu) of EBOV-Kikwit intramuscularly (IM), that platelet counts, prothrombin time (PT), AST, ALT, ALT, LDH, and CPK correlated significantly with time to death and with log10 viral RNA [8]. Similarly, we found in a linear regression model that at 7 dpi, LDH and CPK correlated significantly with time to death and with log10 viral RNA. These findings are not surprising given that Warren et al. [9] showed that in the 1000 pfu IM EBOV-Kikwit rhesus macaque model the course of EBOV viral load is mirrored by the clinical chemistry results in the setting of successful Ebola Virus Disease (EVD) treatment using GS-5734.

In the absence of another large scale human Ebola virus outbreak, the path to licensure of an antiviral in the United States would most likely need to be via the FDA Animal Rule [10], with human data supplementing the animal data. We found that laboratory values in humans and in the IM EBOV-Kikwit rhesus model are strikingly similar, exhibiting changes consistent with systemic inflammatory response syndrome (SIRS) and multi organ injury. Humans and rhesus NHPs both exhibit thrombocytopenia; alterations of serum AST, ALT, blood urea nitrogen (BUN), creatinine, albumin, C-reactive protein (CRP), LDH, PT, aPTT, and CPK. Both humans and rhesus NHPs exhibit high systemic viral load at the peak of disease and in the time leading to death.

We are encouraged that the laboratory values we observed in the IM EBOV-Kikwit NHP model recapitulate what has been reported by Lanini et al in human EVD. We plan to continue further characterizing this model at USAMRIID. We feel that the model is a useful animal model for predicting response in human EVD and is well suited to be utilized to evaluate medical countermeasures under the FDA Animal Rule.

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